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ORIGINAL MEMOIRS.

STUDIES ON THE PATHOLOGY AND ETIOLOGY OF OBSTRUCTIVE HYPERTROPHY AND ATROPHY OF THE PROSTATE GLAND.

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FOR the purpose of this study, there have been placed at my disposal specimens removed by operation in a series of twenty-three cases in the clinic of Dr. Lewis S. Pilcher at the Methodist Episcopal Hospital, and for purposes of comparison various specimens of normal prostates.

There are certain points in the anatomy of the normal prostate which should be made clear, since they are very poorly, and often incorrectly, stated in most of our text-books, and are important in relation to that which is to follow.

The gland is essentially composed of two lateral lobes, connected together in front of the urethra by the anterior commissure, and beneath the urethra by the posterior commissure. The prostatic urethra traverses the gland from base to apex a little in front of its middle. The position of this portion of the urethra varies, sometimes being more anteriorly and again more posteriorly placed. The cortex of the gland is made up almost entirely of non-striped muscular tissue

mixed with a small amount of fibrous tissue, which can be separated from the glandular elements with difficulty. This comprises what is known as the capsule of the prostate. Outside this is an indefinite sheath of fibrous tissue, in which is found the prostatic plexus of veins. Its identification and demonstration are difficult. The ejaculatory ducts and twenty or thirty prostatic ducts open into the prostatic urethra.

The organ is composed of stroma and glandular elements, the exact proportions of which vary. This range of variation is relatively great, in the writer's opinion more so than in any other gland in the body, being affected by age, function, and the calls of nature upon it. According to various careful observers, the glandular elements make up from one-third to five-sixths of the substance of the gland. The very fact of such a discrepancy in the estimates of these men shows how great the variation may be. The gland consists of forty to sixty lobules of the alveolar type. These lobules, however, are not distinct, and are traced with difficulty.

A number of alveoli empty into a single duct, a few of these ducts opening into a larger main duct which opens obliquely into the urethra. The alveoli are lined with columnar epithelium. The stroma is composed of muscular and connective-tissue elements in varying proportions. This, too, is influenced by age and function. Elastic tissue is also present. The small blood-vessels and capillaries run through the stroma. Connective-tissue cells,—especially numerous and large in the young,—plasma cells, and leucocytes are scattered throughout the connective tissue. From the dense capsule, according to Walker,[1] whose studies are among the most complete of recent writers, strong bands of muscular tissue and connective tissue pass into the gland and subdivide, surrounding the lobules. The muscular divisions give to each lobule a distinct circular and longitudinal coat; the circular fibres ramifying among the lobules in a figure-of-eight course; the longitudinal layer lying immediately next to the gland substance, encasing the lobule more or less completely. The connective tissue ramifies among the cellular tissue, forming a

net-work on which the cells rest. The existence of a membrana propria is questionable. The elastic tissue forms a small but important element of the stroma. Arising from a longitudinal sheath of fibres surrounding the urethra, the fibres pass outward and form a net-work around the prostatic ducts, giving to each a distinct sphincter. (Walker.[1]) The fibres extend more deeply into the gland, among the connective-tissue bundles and around the lobules.

PATHOLOGICAL CHANGES.

The specimens which have been studied by us have all been those removed from patients during life, for the relief of urinary obstruction.

I. *Gross.*—In these cases we have found three distinct types of prostates. One the *greatly enlarged, soft prostate;* second, the *relatively small, contracted, hard prostate;* and a third, *mixed type.* I may add here that in cases giving a positive gonorrhœal history each type has been seen. The same is true of the cases giving an absolutely negative gonorrhœal history, and in the cases where there was no cystitis, and also where cystitis was present. Thus of the nineteen cases where there was no gonorrhœal history, the prostate was of the large, soft variety in ten cases, small and hard in three cases, of the mixed type in six cases. Of the gonorrhœal cases, two presented large, soft prostates, and two of the mixed type. Of the cases with cystitis, two of the prostates were hard and contracted, five of the mixed type, and seven of the large, soft variety. Of the cases in which there was no history of venereal disease and no cystitis, one presented a small, hard prostate; three large, soft prostates; and two the mixed type. So it would seem that infection did not in any way influence the variety of the pathological changes.

The *massively hypertrophied prostates* vary greatly in their form, consisting either of an enlargement of both lateral lobes, of one lateral lobe, of the lateral lobes and a median enlargement projecting into the bladder (Figs. 1 and 2),—this is the most common,—or a median enlargement alone.

An enlargement of the posterior commissure is rarely seen, and of the anterior commissure never. The entire gland is surrounded by a thickened capsule of non-striped muscular fibres containing a small amount of fibrous tissue (Figs. 1, 2, and 3). This capsule is thicker and better defined than in the normal prostate; its fibres are more distinct, and it can more easily be stripped away from the gland proper. It entirely surrounds the glandular mass (Figs. 1, 2, and 3), and, covering the portion which projects into the bladder, it lies immediately beneath the mucous membrane lining the bladder (Fig. 1), the sheath being absent here. In the suprapubic operation, when the entire gland is removed, this capsule is not disturbed, but is shelled out with the gland from the sheath covering the prostatic body (Fig. 1). In this way the prostatic plexus of veins is exposed, and dangerous hæmorrhage may occur. In the perineal operation this muscular capsule is opened into, and the hypertrophied glandular masses are shelled out without exposing the veins, and the capsule is left behind. The surface of the hypertrophied prostate is irregular, presenting bulgings and valleys corresponding to the uneven hypertrophy of the glandular, muscular, and connective-tissue elements. In bilateral enlargement the sphincter vesicæ is not destroyed, as it generally is in the other forms. Retention results from purely mechanical means.

The urethra is distorted, depending upon the size, direction, and extent of the hypertrophy (Figs. 2 and 3). It may be lengthened and compressed, its plane depressed downward and backward, and sometimes curved laterally. The mucous membrane lining the prostatic urethra is intimately related to the gland itself, and can only be separated from it with difficulty (Fig. 4).

The size of the obstructing prostate varies from the normal size, 200 to 300 grains, to several ounces. The weight of the largest in the present series was five ounces.

The *atrophic form*, on the other hand, may be even smaller than normal. In the cases of this type operated on by us, the average amount of tissue removed was about 250 grains. In

FIG. 1.—Photograph of hypertrophied prostate removed by suprapubic route. Showing bilateral and median enlargement. At vesical pole, A, the capsule and mucous membrane of the bladder are shown stripped back from the glandular portion of the gland. At B is seen the circular capsule which passes entirely around the gland. Cross-sections at this point are shown in Figs. 2 and 3

FIG. 2.—Photograph of cross-section at B of specimen shown in Fig. 1. Showing capsule, distortion of urethra, and distribution of hypertrophy.

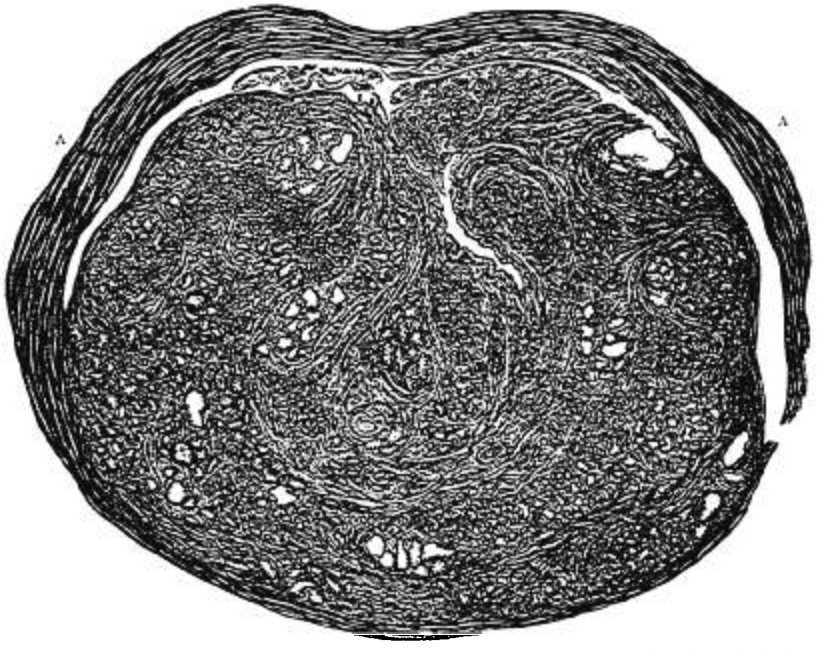

FIG. 3.—Cross-section at B of specimen shown in Fig. 1 slightly magnified. Note relation of capsule A, A, to glandular structure; also distortion of the urethra and distribution of glandular and fibromuscular hypertrophy.

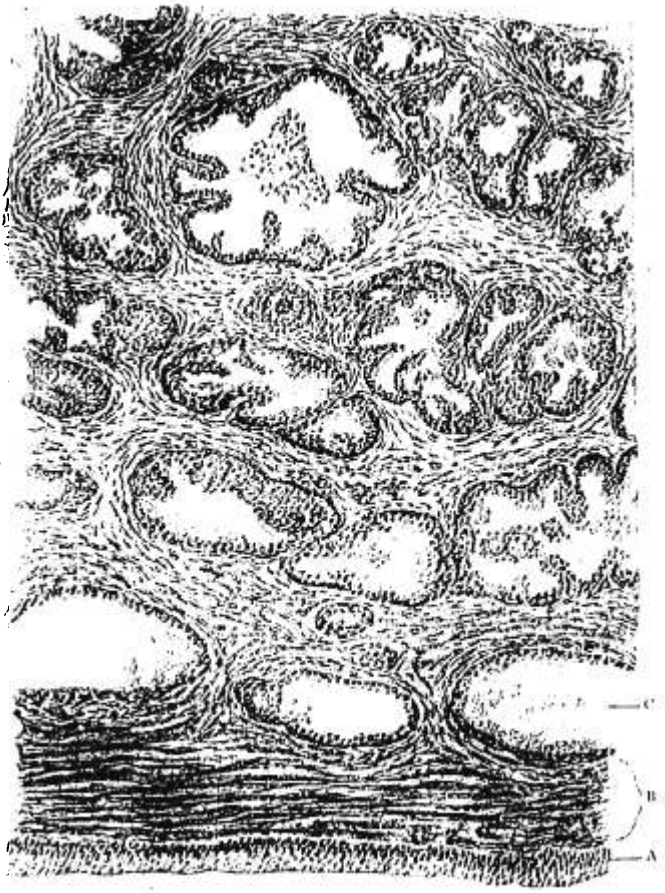

FIG. 4.—Showing relation of the mucosa of the prostatic urethra to the substance of the prostate. Camera lucida drawing from same section as Fig. 3. Note the intimate relation between the epithelial layer, A, and the underlying fibromuscular layer, B, which is not in any way differentiated from the musculo-glandulo-fibrous layer, C, which makes up the bulk of the hypertrophied prostate. In the musculofibrous layer, B, the muscular elements predominate.

these cases the disease affected both lateral lobes, with in some cases a very small median enlargement. The prostate is hard and firm, the capsule densely adherent. The sheath and the fibrous connective tissue of the perineal outlet, in general, are more dense and tough, rendering the identification and isolation of the perineal structures more difficult. The surface of the gland is very irregular. The direction of the urethra is distorted, but not much increased in length. The patients presenting such prostates suffered more from retention than from incontinence.

II. *Microscopical.*—Sections of the hypertrophied prostate vary greatly in the distribution of the pathological changes. The most striking change from the normal is the *relative and absolute increase in the amount of glandular tissue.* All degrees of change from the normal alveoli to the formation of cysts and large adenomatous-like masses are seen (Figs. 5 and 6). The ducts are in many places dilated and filled with retained secretion, often degenerated epithelium, leucocytes, amylaceous bodies, and calculi. These contents may even obstruct the ducts. In the tissue surrounding the ducts are often seen round cells and polymorphonuclear leucocytes. In some places the ducts are seemingly constricted. Laurence[4] found by injecting fluid metal into the urethra, that unless a high pressure was used, the glands in normal prostates could not be injected because of their small caliber. On the other hand, in the hypertrophied prostates the injection was easy and more complete because the terminal (urethral) tubules were enlarged and dilated, and did not obstruct the influx of the metal.

The glands and acini are greatly but unevenly dilated and hypertrophied (Figs. 3 and 4). A whole lobule may be enlarged without any dilatation of the acini, presenting the appearance of an adenoma, but differing from it in that it has a definite, active secretion which is emptied into the urethra by the ducts. A small portion of a lobule or a single acinus may be affected. Crandon[6] explains this fact as due to obstruction of the main duct in the first case, or to the obstruc-

tion of one or more of the smaller ducts, as the case may be. This explanation, however, is very unsatisfactory. Crandon in his article[6] presents an illustration showing a few scattered glandular elements beneath the mucous membrane of the bladder just at the beginning of the urethra, from which it is claimed the median enlargement develops. How can the theory of the obstruction of the ducts of these few scattered glands account for the great median enlargement which is often seen, containing many thousand times more secreting surface than in the normal, and in which there appear no cysts larger than are found in the normal functionating gland? The whole picture is not one of passive dilatation, but of active hyperplasia and hypertrophy (Figs. 3, 4, and 5). The alveoli contain débris, desquamated cells, amyloid bodies, concretions, and often leucocytes; but these, too, are found in normal functionating glands.

My own observations as to the relative change in the amount of muscular tissue in the hypertrophied prostate does not agree entirely with that of other workers. The two coats surrounding the dilated acini do not show as distinct a differentiation as in the young prostate. From the nature of the glandular change, it is natural to suppose that the surrounding tissue will be distorted, but not necessarily changed relatively. It is only when the wall between two adjacent acini becomes thinned down to one or two layers of cells that the muscular fibres disappear (Fig. 5), and only the connective-tissue framework remains. In fact, in many cases the muscular tissue shows a moderate but true hypertrophy.

The amount of connective tissue varies in different specimens. Most observers claim it is everywhere increased, but not relatively as much as the glandular tissue. I cannot entirely agree with this. It is true that in many cases the connective tissue is increased relatively, but sometimes the proportion of muscular hypertrophy is almost as great as the connective-tissue increase (Figs. 4 and 5). Throughout this tissue at different points varying degrees of round-cell infiltration are to be seen. In some cases arteriosclerosis of an

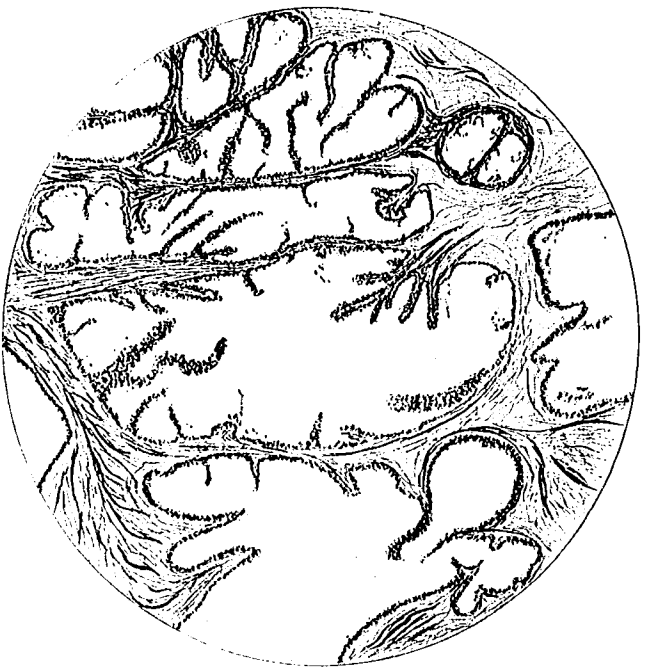

FIG. 5.—Exact drawing from a portion of an hypertrophied and dilated lobule. Showing the thinning out of the musculofibrous stroma. The lighter areas of the stroma represent muscular tissue and the heavier lines connective tissue. In some places the walls separating the acini have disappeared.

(For the drawings from which Figs. 5, 6, 7, and 8 were made, the author is indebted to Dr. Henry G. Webster.)

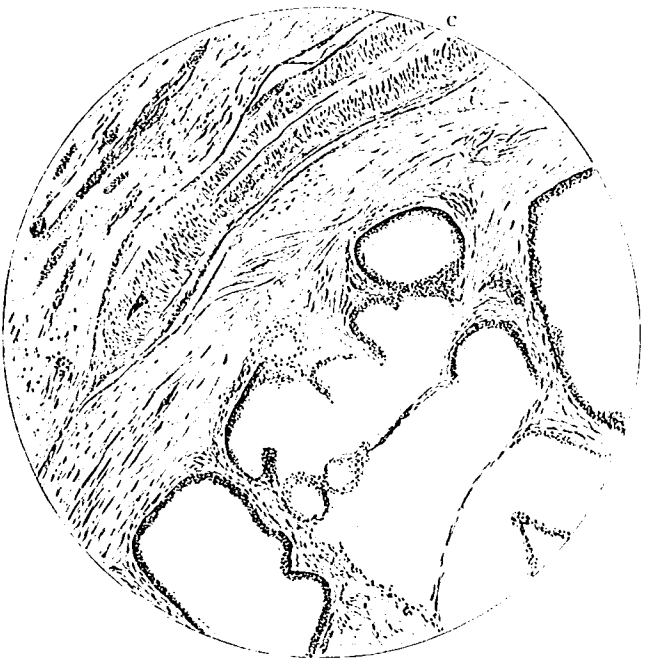

FIG. 6.—Exact drawing from periphery of same lobule as shown in Fig. 5. Showing a sclerosed vessel whose lumen is represented by a single line of endothelial cells, C. Note how the vessel wall is separated from the fibromuscular structures of the lobule, just as the fibromuscular capsule of the gland is from the glandular body itself. Small areas of extravasated blood and round cell infiltration are seen.

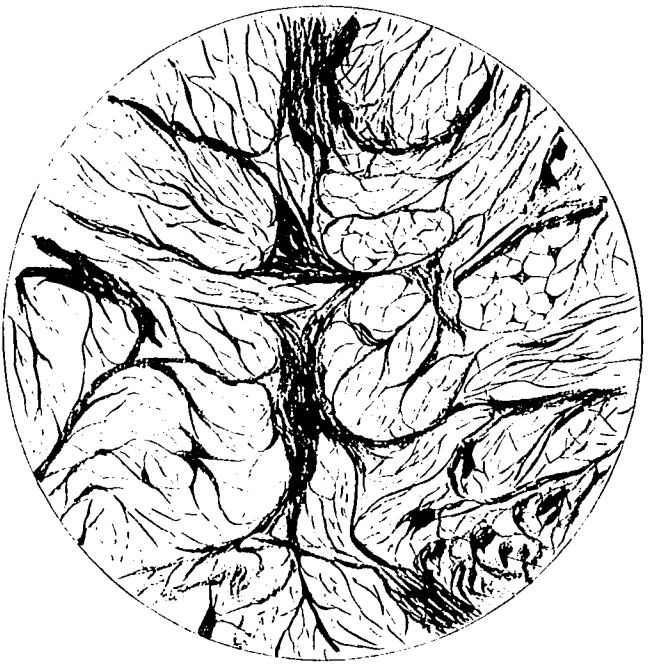

FIG. 7.—Exact drawing from a section of a small atrophic prostate which caused obstruction. Showing the absence of glandular elements and the great relative increase in the muscular elements. (The lighter areas represent muscular tissue, the heavier lines connective tissue.)

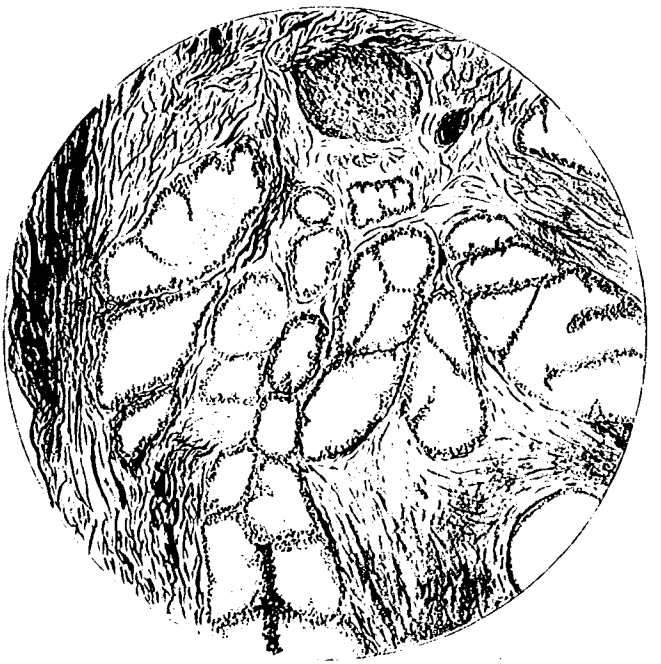

FIG. 8.—Section from mixed type of hypertrophy of prostate. Darker lines representing connective tissue and lighter areas unstriped muscular tissue between and around the glandular acini.

advanced stage is present (Fig. 6). In many of our cases there were seen areas of extravasated blood (Fig. 6). Again are seen areas of normal tissue.

In the *atrophic* prostates two forms have been observed. The *first* in which the glandular elements are decreased and smaller than normal. In these prostates the amount of muscular tissue present seems to exceed the amount of new connective tissue, which in some cases is relatively diminished. In one case the predominance of muscular tissue was very marked (Fig. 7). The *second* form presents a combination of compressed glands which predominate, and a few dilated hypertrophied lobules which, however, never reach any considerable size (Fig. 8).

It is interesting to note here that Daniel,[5] who examined a series of prostates removed post-mortem from the bodies of patients not complaining of prostatic symptoms, *i.e.*, were devoid of obvious enlargement, and who in many cases were under thirty years of age, found exactly the same pathological appearances, with some exceptions, as have been described.

Etiology.—Ciechanowski,[7] quoted by Greene and Brooks,[8] and Crandon[6] concludes that "the common starting-point of the enlargement and certain forms of atrophy of the prostate is to be sought for in the productive connective-tissue processes which occur in the stroma."

Before accepting this theory, consider first the life history of the prostatic body. Heisler ("Text-Book of Embryology," 1899, p. 234) tells us that "in the twelfth week the future prostatic urethra acquires very thick muscular walls, and the original epithelial tube pouches out into the muscular tissue in the form of little sacs, the lining cells of which assume the character of secreting epithelium. In this way is produced the aggregation of muscular and glandular tissue known as the prostate gland." Until functional activity begins, the glandular elements appear as simple branched tubular glands resembling the other urethral glands and forming an insignificant part of the prostatic body. Then the function of the gland is demanded and the glandular elements multiply. The simple

branched tubular glands become most complex in their structure, and, just as in the female breast when functionating, become separated into distinct lobules. There then arises a new demand for expression of the glandular secretion; therefore the muscular elements increase and become better differentiated, and if the prostate be examined at this time, it will be seen to be essentially a musculo-glandular body, the acini filled with secretion, degenerated epithelial elements, amylaceous bodies, etc., just as in the functionating breast. It is an actively functionating gland, varying greatly in different individuals, corresponding to the demands of its possessor upon its function. In one case we may have a glandulo-muscular body, in another a musculo-fibro-glandular body, and so on. As age advances, conditions change. In some, glandular activity ceases early, but generally not until after the degenerative changes incident to old age have made their appearance. In eight of our cases, where we have ascertained the age to which sexual intercourse was continued, the average was sixty-seven years. It is fair to suppose, then, that in these cases, at least, glandular function was kept up, and that possibly glandular hypertrophy took place in a perfectly natural way, influenced and governed by advancing age. From a study of these prostates, it has seemed to us that the hypertrophy was due more to glandular overgrowth, distorted and increased by the degenerative changes of old age, than to the influence of any extrinsic inflammatory agency constricting the ducts and causing their dilatation. The question may be asked why this does not take place in all cases. That is as difficult to answer as it is to explain why fibroids, myomata, and adenomata develop in the uterus of one woman and not in that of another. We believe that it is not necessarily the length of functional activity of the gland and the age of the individual which cause this hypertrophy, but that it is a glandular overgrowth influenced by the degenerative changes of old age in an actively functionating gland which produces the change. A previous gonorrhœal infection, or any other inflammatory process, may influence the development of the disease.

That, however, *gonorrhœal infection* is always, or even a frequent, cause of the pathological changes which have been described, is a theory which needs much stronger proof before it can be accepted. It is but fair to suppose, too, that other causes may influence this overgrowth. Excessive venery, over-indulgence in alcohol, masturbation, protracted indulgence in withdrawal, sexual excesses, perverted indulgences, horse-back riding, long-continued sedentary habits, constipation, and climatic exposures, all may be considered as possible contributing etiological factors.

The following are the reasons advanced by Ciechanowski (Crandon,[6] *loc. cit.*, p. 843) for his belief in the correlation of gonorrhœa and the enlarged prostate.

(1) The frequency of gonorrhœa;

(2) The frequency of chronic gonorrhœa in the posterior urethra and prostate, *i.e.*, in 1070 cases the process was in the deep urethra in 424;

(3) The frequency of cystitis; and, lastly,

(4) The only domestic animal that suffers from enlarged prostate is the dog; and the male dog, too, seems to be the only animal that has a true purulent urethritis which is infectious.

Compare these reasons with the following histories and facts.

Case I.—A gentleman, aged seventy-four years, was admitted to the hospital in August, 1903. First experienced difficulty in passing water at the age of fifty-two. Up to this time he states absolutely that he never had had intercourse with any woman. At the age of fifty-three he had intercourse with a woman for the first time. When he was fifty-four he began to use a catheter occasionally to empty his bladder. Married at age of fifty-six. His wife has borne him three children. Continued his marital relations to age of seventy-three. In his seventy-fourth year we removed a large, soft prostate weighing two ounces.

Case II.—A gentleman, aged fifty-seven years. Always has lived a moderate life. Never used tobacco or alcohol. Denies absolutely gonorrhœa or any venereal disease. Never had inter-

course with any woman excepting his wife. Married at age of twenty-five years. Moderate indulgence in coitus. Is a very intelligent man, and had no reason to conceal anything. Prostatic and vesical calculus symptoms for four years. October, 1904, removed a prostate weighing 750 grains, after removal of multiple calculi from bladder.

CASE III.—A gentleman, aged sixty-six years; never had gonorrhœa or other venereal disease. Never had intercourse with any other woman than his wife. Never used tobacco or alcohol. Married at age of thirty-seven. Prostatic symptoms at age of sixty-two. Catheter life for four years; marked cystitis; by prostatectomy a moderately enlarged prostate weighing 300 grains removed.

Of our twenty-three cases, fourteen absolutely denied any venereal disease; four had in their earlier years suffered from gonorrhœa; and in the remaining five cases no history of gonorrhœa could be elicited at the time the history was taken, but they have not been asked since concerning it.

In this series of cases we have had to deal with men most of whom were far above the general average in regard to their habits, mental attainments, social standing, and education. If the history of cases is ever to be depended upon, it certainly seems fair to accept the statements of these men as truthful.

RÉSUMÉ.

1. Pathologically there are three types of prostates causing urinary obstruction: (*a*) The large, soft type, (*b*) the hard, small, contracted type, and (*c*) the mixed type.

2. Infection does not influence the variety of the pathological change.

3. The contracted form of prostate is not a secondary stage of the large, soft type of hypertrophied prostate, but is distinct from it.

4. In many cases of hypertrophy of the prostate there is present a true muscular hypertrophy.

5. In some of the atrophic cases the glandular elements

are relatively diminished and the muscular elements relatively increased.

6. Gonorrhœa is not an important etiological factor in the production of this disease, and there is no necessity for assuming it to be.

7. The theory of obstruction to the ducts causing passive dilatation of the glandular elements, as advanced by Ciechanowski and Crandon, does not satisfactorily explain the pathological findings.

8. Hypertrophy of the prostate results from glandular overgrowth, influenced by the degenerative changes of old age, and other agents which tend to produce the formation of fibrous connective tissue in an actively functionating gland.

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